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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
CANELLA, KAREN A

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 04/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/914,662	JORDAN, ANDREAS	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-3 and 6-17* is/are pending in the application.

4a) Of the above claim(s) *9-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-3,6-8 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 2, 3 and 8 have been amended. Claim 4 has been canceled. Claim 17 has been added. Claims 1-3 and 6-17 are pending. Claims 9-16, drawn to a non-elected invention, remain withdrawn from consideration. Claims 1-3, 6-8 and 17 are under consideration.

Sections of Title 35, U.S. code, not found in this action can be found in a previous action.

Claims 1-3, 6-8 and 17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "the culture medium" in claims 1 and 17, lacks antecedent basis with the claim which only refers to "a medium".

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 8 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re wands, 858 F.2d 731, 737.8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Claim 8 requires that the method of claim 1 be carrier out with the culture medium as set.

forth in claim 8. Claim 1 encompasses all types of cancer cells residing in solid tissues which can be separated by mechanical fragmentation. This includes all adenocarcinomas, carcinomas, sarcomas, melanomas and gliomas and other nervous system tissues. It is noted that culture conditions for each tumor cell type requires optimization. Each ingredient in claim 8 is specified as a range of weight per volume amounts. Claim 8 requires 7 inorganic salts, 21 amino acids, 19 vitamins and 6 other ingredients, all of which require optimization to a value within the specified range. It is noted that out of the "classic media" formulations, such as RPMI, MEM, DMEM, F-12K, DMEM-F12, L-15, McCoy's 5A, Iscove's Modified Dulbecco's and Hybri-Care, only RPMI requires $Ca(No_3)_2$, and none require both $Ca(NO_3)_2$ and $CaCl_2$. It would be undue experimentation to one of skill in the art to practice the invention of claim 8 for every type of cancerous tissue encompassed by claim 1 because each of the ingredients of claim 8 require optimization for each tumor type, none of the ingredients are specified without a range. Claim 1 reads on tumor biopsy specimens taken from patients. Thus, one of skill in the art would be restricted in the type of material used for the optimization, because it is well know that tumor cell lines have different requirements for viability than tumor explants or biopsy samples. Thus, one of skill in the art would not have unlimited amounts of tissue to commit to optimization studies. Given the breath of both of claims 1 and 8, and the lack of specific teachings in the specification which would serve to direct one of skill in the art to particular set values of the different ingredients of claim 8 to a particular tumor type, such as breast adenocarcinoma or melanoma, one of skill in the art would be subject to undue experimentation in order to carry out the method of claim 8.

Claims 1-3, 6, 7 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kornblith (WO 98/02038, cited in the previous Office action) in view of the abstract of Joyce et al (Pathology, 1985, Vol. 17, pp. 355-359, cited in a previous Office action), Adams et al (U.S. 6,376,169, cited in a previous Office action), Freshney (Culture of Animal Cells, 3rd Ed., 1994, pages 73, 79, 101-102 and 263, cited in a previous Office action),Yen-Maguire et al (WO 91/117240) and any of the abstracts of Ogden et al (Journal of Oral Pathology and Medicine, 1992, Vol. 21, pp, 17-20), Ellis et al (journal of Respiratory and Critical Care Medicine, 1994, Vol. 149, pp. 118-122) or Jeng et al (Journal of Surgical Research, 1996, vol. 61, pp. 477-481).

Claim 1 is drawn to a method of cultivating cancer cells from human tissue for molecular-biological mass screenings wherein a tissue sample is locally separated into disc segments by sequential and parallel mechanical splitting based on the heterogeneous structure of tumor cells, normal cells and contaminants, and wherein said separated tissue sample segments are further split into tissue fragments, and wherein said small, separated tissue fragments and fluids of the locally separated tissue sample segments are selectively cultivated in a specific medium and under predefined cultivation conditions and under suppression of the disturbing influence of normal cells and contaminants and wherein tissue fragments and fluids obtained form the locally separated tissue sample segments are cultivated separately in cell culture bottles filled with said medium and coated with a biomatrix substrate in a 0.01% to 3% oxygen atmosphere, a 0.1% to 5% carbon dioxide atmosphere at a humidity of 100% and temperatures in the range of 30 to 36.5 degrees and wherein said tissue sample is temporarily placed in a medium together with adhering erythrocytes until the tissue sample fragments are produces ad wherein the tissue sample is kept in the culture medium for a minimum of 2 hours but not longer than 24 hours at a temperature in the range from 4 degrees C to 12 degrees C to get adapted to said medium. Claim 2 embodies the method of claim 1 wherein said tissue sample is obtained from fine needle, aspiration intraoperative biopsies or a resection sample. Claim 3 embodies the method of claim 2 wherein the culture medium for storage of freshly taken sample and the medium to be used for cultivating the tumor cells are identical.

Claim 6 embodies the method of claim 5 wherein the medium in the culture bottle is replaced by fresh medium of the same composition some time after initial establishment of the cell culture and completed adhesion. Claim 7 embodies the method of claim 6 wherein the medium is replaced with a medium comprising either the same or a reduced portion of antibiotics depending on the presence of contaminants such as bacteria and fungi.

Claim 37 is drawn to a method of cultivating cancer cells from human tissue for molecular-biological mass screenings wherein a tissue sample is locally separated into disc segments by sequential and parallel mechanical splitting based on the heterogeneous structure of tumor cells, normal cells and contaminants, and wherein said separated tissue sample segments are further split into tissue fragments, and wherein said small, separated tissue fragments and fluids of the locally separated tissue sample segments are selectively cultivated in a specific

medium and under predefined cultivation conditions and under suppression of the disturbing influence of normal cells and contaminants and wherein tissue fragments and fluids obtained form the locally separated tissue sample segments are cultivated separately in cell culture bottles filled with said medium and coated with a biomatrix substrate in a 0.01% to 3% oxygen atmosphere, a 0.1% to 5% carbon dioxide atmosphere at a humidity of 100% and temperatures in the range of 30 to 36.5 degrees, and wherein said tissue sample is obtained from fine needle, aspiration, intraoperative biopsies or a resection sample and said tissue sample is temporarily placed in a medium together with adhering erythrocytes, wherein the tissue sample is kept in the culture medium for a minimum of 2 hours but not longer than 24 hours at a temperature in the range of 4 degrees C to 12 degrees C to get adapted to said medium.

Kornblith teaches a method for screening a multiple of candidate therapeutic or chemotherapeutic agents for efficacy as to a specific patient, in which a tissue sample from the patient is harvested, cultured and separately exposed to a plurality of treatments and/or therapeutic agents for the purpose of objectively identifying the best treatment for the cultured cells obtained from the patient (page 2, lines 28-35), thus fulfilling the limitation of new claim 17 requiring an interoperative biopsy or a resection sample.. Kornblith teaches that a particularly important tissue sample preparation technique is the initial preparation of cohesive multicellular particulates of the tissue sample, rather than enzymatically dissociated cell suspensions or preparations, for initial tissue culture monolayer preparation and that by maintaining malignant cells within a multicellular particulate of the originating tissue, growth of the malignant cells themselves is facilitated versus the overgrowth of fibroblasts or other cells which tends to occur when suspended tumor cells are grown in culture (page 3, lines 2-14). Kornblith teaches that practical monolayers of cells may thus be formed to enable meaningful screening of a plurality of treatments and/or agents (page 3, lines 20-23). Kornblith teaches that the sample is a tumor biopsy of > 100 mg of nonnecrotic, non-contaminated tissue is harvested from the patient by any suitable biopsy or surgical procedure known in the art (page 4, lines 30-35). Kornblith teaches that the tumor is removed, under sterile conditions, from the shipping container and is minced with sterile scissors but if the specimen arrives already minced, the individual tumor pieces should be divided into four groups (page 5, lines 2-6). Kornblith teaches that each undivided tissue quarter is then placed in 3 ml sterile growth medium (Standard F-10 medium containing

17% calf serum and a standard amount of Penicillin and Streptomycin) and systematically minced by using two sterile scalpels in a scissor-like motion, or mechanically equivalent manual or automated opposing incisor blades and that said cross-cutting motion is important because the technique creates smooth cut edges on the resulting tumor multicellular particulates (page 5, lines 6-15). Kornblith teaches that preferably the tumor particulates each measure 1 mm3 and that after each tumor quarter has been minced, the particles are plated in culture flasks using sterile Pasteur pipettes (9 explants per T-25 or 20 particulates per T-75 flask, page 5, lines 15-19). Kornblith teaches that the explants should be evenly distributed across the bottom surface of the flask, with initial inverted incubation in a 37 degree C. incubator for 5-10 minutes, followed by addition of about 5-10 ml sterile growth medium and further incubation in the normal, non-inverted position (page 5, lines 21-26). Kornblith teaches that the flasks should be checked daily for growth and contamination and weekly removal and replacement of 5 ml of growth medium (page 5, lines 27-28). The disclosure of Kornblith fulfills the specific embodiments of cultivation of separated tissue fragments and fluids because the mincing of the tissue segment while in sterile growth medium, and the propagation of the initial culture from said medium would inherently comprise any fluids from the locally separated tissue sample segment. The teachings of Kornblith fulfills the specific embodiments of cultivation under suppression of the disturbing influences of normal cells and contaminants because Kornblith teaches that the growth of the malignant cells is facilitated versus the overgrowth of fibroblasts or other cells which tends to occur when suspended tumor cells are grown in culture, therefore the growth of the undesired cells is suppressed. The teachings of Kornblith anticipates the specific embodiments of claim 6 and 7 because Kornblith directs the inspection of the flasks for microbial contamination, and the weekly replacement of the growth medium. Kornblith does not teach the growth of the cells under conditions of 0.01%-3% oxygen, 0.1% to 5% carbon dioxide, nor does Kornblith specifically teach the coating of the culture bottles with biomatrix substrate, or the growth of the culture at a temperature of 30 to 36.5 degrees C, nor does Kornblith specifically teach that the transport medium and the cultivation medium are the same, or the maintenance of the tumor tissue in the transport medium at 4 degrees to 12 degrees for 2 hours to 24 hours in order to adapt the tumor tissue to the medium..

Adams et al teach the culture of tumor cell lines (column 13, line 8 and line 26) under hypoxic conditions of 2-10% oxygen and 5% carbon dioxide (column 13, lines 49-54). The 2% oxygen and the 5% carbon dioxide are within the claimed ranges.

The abstract of Joyce et al teaches that tumor growth in hypoxic semi-solid culture conditions was enhanced due to the recruitment of additional colony forming cells.

Freshney teaches that human tumor cells in clonogenic assays do better in less than normal atmospheric oxygen (page 79, second column, lines 12-15), Freshney also teaches that the recommended temperature for most human and warm blooded animal cells is 36.5, which is a little lower than the 37 degree body temperature for reasons of safety because overheating is a more serious problem than under heating (pages 101-102, bridging sentence). Freshney also teaches that cell attachment and growth can be improved by coating with a biomatrix such as matrigel which is known to support the growth of malignant cells (page 73, under the heading of "Treated Surfaces, especially column 2 , lines 8-13). Freshney also teaches that cells may be transported in medium (page 264, second column, lines 3-8).

Yen-Maguire et al teach that in vitro drug response assays are performed in university hospitals and a few specialized service centers which generally require the transportation of the specimen, resulting in a loss of often more than 24 hours before specimen processing can begin. Yen-Maguire et al teach that within this 24 hour period, specimen viability declines significantly (page 9, lines 26-31), thus fulfilling the specific embodiments of "no longer than 24 hours" as recited in claims 1 and 17.

Any of the abstracts of Ogden et al (journal of Oral Pathology and Medicine, 1992, Vol. 21, pp, 17-20), Ellis et al (journal of Respiratory and Critical Care Medicine, 1994, Vol. 149, pp. 118-122) or Jeng et al (Journal of surgical Research, 1996, vol. 61, pp. 477-481) teach that biopsy material is held in medium at 4 degrees C.

It would have been prima facie obvious at the time the claimed invention was made to grow the tissue segments produced from tumors by the method of Kornblith in an atmosphere of 2% oxygen and 5% carbon dioxide at a temperature of 36.5 degrees, in culture bottles coated with matrigel. One of skill in the art would be motivated to do so by the teachings of both Freshney and the abstract of Joyce indicating that tumor cells grow better under less than normal oxygen conditions or hypoxic conditions and on a matrigel matrix, and the further teachings of

Adams et al on the 2% oxygen and 5% carbon dioxide concentration for growing human tumor cells under hypoxic conditions. One of skill in the art would be motivated to grow the cells at 36.5 degrees rather than at 37 degrees by the recommendation of Freshney regarding the desirability of avoiding overheating.

It would have also been prima facie obvious at the time the claimed invention was made to provide the surgeon with medium that would be used for cultivation so that the biopsy sample(s) may be transported in said medium. One of skill in the art would be motivated to do so in order that all samples collected from various sources would be exposed to the same nutrient conditions ex vivo. One of skill in the art would also be motivated to do so in order that the tumor sample would not undergo two separate adjustments to osmolality, pH and nutrients in two different media. One of skill in the art would be motivated to try to preserve the viability of the tumor specimen. Further it would be prima facie obvious to replace the medium. Also, one of skill in the art would have been motivated to hold the tumor tissue in transport medium no longer than 24 hours and 4 degrees C to avoid the decline of viability in said tumor cells as per the teachings of Yen-Maguire et al and what is well known in the art as exemplified by the abstracts of Ogden et al (journal of Oral Pathology and Medicine, 1992, Vol. 21, pp, 17-20), Ellis et al (journal of Respiratory and Critical Care Medicine, 1994, Vol. 149, pp. 118-122) or Jeng et al (Journal of surgical Research, 1996, vol. 61, pp. 477-481).

All other rejections and objections are withdrawn in light of applicants amendments.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 11 am to 10 pm, except Wed, Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
4/10/2006

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